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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,693	02/02/2001	Mike A. Clark	PHOE-0060	9010

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/775,693	CLARK ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 16 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *22 June 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *none*.

Claim(s) rejected: *1-2, 6-7, 27, 31-36*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-2, 6-7, 27, 31-36 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 103

Rejection under 35 USC 103 of claims 1-2, 6-7, 27, 31-36 pertaining to being obvious over US 5,804,183 in view of Takaku, H et al, 1995, Jpn. J Cancer Res, 86: 840-846, IDS# AM, in paper No:6, on 06/19/01, Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01 , and Oyanagi, K et al, 1986, Tohoku J Exp Med (Japan), 148 (4): 385-91, remains for reasons already of record in paper of 12/22/03.

Applicant asserts that the Office Action's assertion of obviousness is based upon an incorrect reading of the cited references, which, in fact, do not contain the teachings attributed to them by the Office Action. Applicant argues that the Office Action asserts that the AD sensitivity of various tumor cells is attributed to the reduced level of ASS expression, as taught by Sugimura, et al, however, the Sugimura reference teaches only that arginine deiminase sensitivity of **melanoma** cells **may** be attributed to reduced levels of argininosuccinate synthetase. Applicant argues that notably, the reference states that one melanoma cell line (G361) "exhibited a significant level of ASS gene expression. . .(but) was still highly sensitive to the growth inhibitory activity of AD." (See

page 194, second column). Applicant argues that the reference, therefore, does not teach that arginine deiminase sensitivity can be definitively attributed to reduced argininosuccinate synthetase expression in melanoma cells.

Applicant argues that moreover, the reference contains no teachings whatsoever with respect to whether arginine deiminase sensitivity can be attributed to reduced levels of argininosuccinate synthetase in tumor cell types other than melanoma.

Applicant argues that the Takaku reference does not teach or suggest that the arginine deiminase-sensitive tumor cell lines tested (or any tumor cells lines for that matter) are deficient or have reduced levels of argininosuccinate synthetase. Applicant argues that in fact, the reference states that "the mechanism by which [a-AD] causes inhibition of tumor cell growth is still unclear." (See page 840, second column).

Applicant's arguments set forth in paper of 03/16/04 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant arguments, Sugimura et al teach that as expected, RT-PCR analysis for ASS (argininosuccinate synthetase) gene transcripts directly demonstrated the low level of ASS gene expression in human melanoma cell lines exhibiting high sensitivity to AD (arginine deiminase) (p.194, second column, lines 5-8 of second paragraph). Thus, one would conclude that there is clear correlation between the low level of ASS gene expression in human melanoma cell lines and high sensitivity to AD based on the teaching of Sugimura et al.

Further, it is noted that from five melanoma cell lines, expression of ASS gene is almost absent in four cell lines and at low level in one cell line G361, wherein the

expression of G361 is 1/5 lower than that of the positive control (Sugimura et al ,abstract, lines 9-12, figure 4 a-c, p.194, first column, last paragraph bridging second column). Thus the statement by Sugimura et al that one melanoma cell line (G361) "exhibited a significant level of ASS gene expression. . .(but) was still highly sensitive to the growth inhibitory activity of AD" indicates that even a reduction of ASS expression to the level of 1/5 lower than that of the positive control still confers the sensitivity to AD as compared to the control.

This correlation between high level of sensitivity to AD and low level of ASS is even shown in some normal cells that have extremely low level of ASS, such as human peripheral blood lymphocytes (Sugimura et al, p.191, second column, last four lines bridging p.192).

Further, in addition to the teaching of Sugimura et al concerning the effectiveness of AD as a growth inhibitor of melanoma cell lines, Takaku et al teach that AD has been successfully used for in vivo treating of mice implanted with four kinds of tumor cell lines, hepatoma, colon carcinoma, sarcoma and melanoma (p.840, first column, lines 5-11 of second paragraph).

Moreover, Takaku teach mechanism of growth inhibition of AD, i.e. AD depletes essential nutrient L-arginine, and blocking the polyamine biosynthesis pathway, and not to the production of ammonia or L-citrulline (abstract, and page 843, second column, under tumor cell growth mechanism of a-AD, bridging page 844). It is noted that L-arginine is essential for the survival of many mammalian cells, and is synthesized from

L-citrulline by argininosuccinate synthetase and argininosuccinate lyase (Sugimura et al, figure 1 on page 191, and second column of page 191).

Further, the statement by Takaku et al that "the mechanism by which [a-AD] causes inhibition of tumor cell growth is still unclear" (page 840, second column), is in the introduction section of the paper, and it could be reasonably interpreted as meaning that the mechanism by which [a-AD] causes inhibition of tumor cell growth was still unclear until the study by Takaku et al, in view of the data taught by Takaku et al, which clearly show the mechanism of growth inhibition of AD, and as indicated by the title of the reference by Takaku et al.

Applicant argues that the Filpula patent cites the Sugimura reference for the proposition that melanomas are deficient in argininosuccinate synthetase. Applicant argues that as previously discussed, the Sugimura reference does not teach that arginine deiminase sensitivity can be definitively attributed to reduced argininosuccinate synthetase expression. Applicant further argues that the Filpula patent fails to suggest or teach that arginine deiminase sensitivity can be attributed to reduced levels of argininosuccinate synthetase in tumor cell types other than melanoma.

The arguments are not found to be persuasive. Sugimura et al teach that as expected, RT-PCR analysis for ASS (argininosuccinate synthetase) gene transcripts directly demonstrated the low level of ASS gene expression in human melanoma cell lines exhibiting high sensitivity to AD (arginine deiminase) (p.194, second column, lines 5-8 of second paragraph), supra. Thus, one would conclude that there is clear

correlation between the low level of ASS gene expression in human melanoma cell lines and high sensitivity to AD based on the teaching of Sugimura et al.

Further, in addition to the teaching of Sugimura et al concerning the effectiveness of AD as a growth inhibitor of melanoma cell lines, Takaku et al teach that AD has been successfully used for in vivo treating of mice implanted with four kinds of tumor cell lines, hepatoma, colon carcinoma, sarcoma and melanoma (p.840, first column, lines 5-11 of second paragraph), supra.

Applicant argues that the Oyanagi reference fails to teach or suggest that cancers such as carcinoma, melanoma, or hepatoma are deficient in, or have reduced levels of argininosuccinate synthetase. Applicant argues that the reference fails to teach or suggest that any type of cancer cell, much less carcinoma, melanoma, or hepatoma, is deficient in, or has reduced levels of, argininosuccinate synthetase.

The arguments are not found to be persuasive. Oyanagi et al teach that a patient, patient 2, who died of hepatoma, has citrullinemia, a disease caused by deficiency of argininosuccinate synthetase in liver tissue (abstract, and page 385, last paragraph, bridging page 386).

Applicant argues that Applicant is the first to demonstrate that tumor cells that are sensitive to arginine deiminase exhibit sensitivity because the cells lack argininosuccinate synthethase. Applicant argues that the remaining possibilities, lack of argininosuccinate lyase or citrulline transporter molecules, were not excluded prior to Applicants' efforts.

Applicant argues that the cited references do not teach or suggest all the limitations of the claims. Applicant argues that there is no motivation to combine the references, and that much more is required than the mere conclusory statement by the Examiner that the idea of combining the above references cleary flows logically from their having been individually taught by in the art. Applicant argues that it must be based on objective evidence of record.

The arguments are not found to be persuasive. From the teaching of Sugimura et al one would conclude that there is a clear correlation between the low level of ASS gene expression in human melanoma cell lines and high sensitivity to AD.

In view of a clear correlation between the low level of ASS gene expression in human melanoma cell lines and high sensitivity to AD, based on the teaching of Sugimura et al, and in view that not all tumor cells are susceptible to arginine deprivation (AD) therapy, and further in view that cancers such as carcinoma, melanoma or hepatoma that have been successfully treated by arginine deprivation (AD) therapy, all are deficient in or have reduced level of arginosuccinate synthetase, as taught by US 5,804,183, Takaku et al, and Oyanagi et al, it would have been obvious to identifying cancer patients susceptible to arginine deprivation therapy, comprising detecting the presence or absence of arginosuccinate synthetase protein in a cancerous tumor sample.

In other words, one would have been motivated to identify cancer patients that could be treated by arginine deprivation (AD) therapy, because not all tumor cells could be treated with arginosuccinate synthetase, as taugh by Sugimura et al. Further, one

would have been motivated to identify cancer patients that could be treated by arginine deprivation (AD) therapy, by detecting the level of arginosuccinate synthetase, because the reduced level of arginosuccinate synthetase is correlated with susceptibility to arginine deprivation (AD) therapy, as taught by Sugimura et al, US 5,804,183, Takaku et al, and Oyanagi et al.

The motivation is to identify cancer patients that could be treated by arginine deprivation (AD) therapy for commercial benefit.

Thus all limitations of the claims are met.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

August 25, 2004